

**REMARKS**

Applicants request that this application be reconsidered in view of the amendments above and the remarks below. A favorable action is requested.

**Claim Amendments**

Claims 1, 2 and 3 have been amended by deleting the word “directly” and adding the term “without use of an affinity group.” Support for this amendment may be found throughout the specification. All of the differential isotope labeled reagents described in the instant application are chemical compounds that contain at least one isotope. See, for example, Table 1, page 19, [0097]. The terms “wherein the molecules are derivatized prior to analysis” and “of the molecules” have also been added. This amendment is requested to clarify that it is the derivatives that are examined by mass spectrometry as opposed to the molecules prior to derivatization. Claim 2 has been further amended by deleting the word “differential.” Claims 2 and 3 have been amended by deleting the word “its.”

Claims 4, 5, 6, 8, 15, 18, 21 and 28 have been amended by adding the term “any one of” to put the claims in proper multiple dependent format.

Claims 7, 9, 11, 18, 20, 21 and 23 have been amended to correct the Markush group language.

Claim 6 has been amended by deleting dependency to claim 4 to overcome the claim objection discussed below.

Claim 19 has been amended by adding the term “sample comprises a protein having an amine and the protein is” for clarity.

Claim 20 has been amended by substituting “proteins” with “protein” which was a typographical error.

Claims 24, 25 and 26 have been re-written. The words "directly" and "its" have been deleted. The term "without use of an affinity group" has been added. These amendments mirror those in claims 1, 2, and 3. Finally, the term "derivatives of" has been added. Claim 25 has been further amended by deleting the word "differential". Both of these amendments are requested to clarify the claim language.

Claim 27 has been re-written to recite the method steps of claim 1.

Claim 29 has been amended by deleting the words "directly" and "its" and deleting the term "derivatives of the." The terms "derivatives of molecules, wherein the molecules have an amine bearing an active hydrogen, and wherein the molecules come from two or more," "without use of an affinity group", "of the molecules", "from each of the extracts", "differentially" and "of the molecules in the extracts into fractions" have been added. Amendments to claim 29 mirror those amendments in other claims described above.

Claims 30 and 31 have been added. They are directed to use of a mass spectrometer reciting the method steps of claims 2 and 3, respectively.

Applicants hereby reserve the right to file a continuation or divisional application on the subject claimed prior to this amendment. Applicants submit that no new matter has been added by these amendments and hereby request their entry. Claim 28 is withdrawn and Claims 1-27 and 29-31 are now pending in the application.

#### **Information Disclosure Statement**

Applicants note that the Information Disclosure Statement filed on May 9, 2005 failed to comply with 37 C.F.R. §1.98(a)(1). According to Applicants records, the following items were submitted via first class mail:

1. First Information Disclosure Statement (3 pgs.)
2. PTO Form SB/08 (3 pgs.)

3. Twenty-one (21) references as cited on SB/08 (3 pgs.)
4. International Search Report (PCT/CA03/01072) (7 pgs.)
5. Return Postcard
6. Check in the amount of \$180.00.

Applicants presume that the PTO Form SB/08 was inadvertently separated from the other items in the filing. A copy of the entire filing is re-presented with this filing, along with the date-stamped postcard. Applicants submit that this Information Disclosure Statement complied with 37 C.F.R. §1.98(a)(1). The Examiner is requested to consider these references. Should the Examiner require anything further, the Examiner is respectfully requested to telephone the undersigned.

#### **Claim Objection**

Claim 6 is objected under 37 C.F.R. §1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Claim 6 has been amended to be dependent only on claims 1, 2 and 3. Claims 1, 2 and 3 are not multiple dependent claims. As such, Applicants request that this objection be withdrawn.

#### **Claim Rejections under 35 U.S.C. §101**

Claim 27 is rejected under 35 U.S.C. §101 because the claim allegedly recites a use, without setting forth any steps involved in the process, results in an improper definition of a process.

In order to overcome this rejection, Applicants have amended claim 27 to recite the method steps analogous to those in claim 1. Applicants have also added new claims 30 and 31 directed to a use of a mass spectrometer reciting analogous method steps of claims 2 and 3, respectively. Upon entry of the amendment, Applicants respectfully request that this rejection be withdrawn.

**Claim Rejections under 35 U.S.C. §112, first paragraph**

Claims 1-3, 24-27 and 29 stand rejected for failing to comply with the written description requirement. Specifically, the claims contain the terms "direct labeling" and "directly labeling", which the Examiner states are not described in the specification.

Without acquiescing the rejection, Applicants have removed the terms "direct labeling" and "directly labeling" from claims 1-3, 24-27 and 29. Applicants have added the term "without use of an affinity group" to claims 1, 2, 3, 24-26 and 29. Applicants respect that this rejection be withdrawn.

**Claim Rejections under 35 U.S.C. §112, second paragraph**

Claims 1-27 and 29 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of the rejections under 35 U.S.C. §112, second paragraph, will be individually addressed below.

(i) Applicants have clarified that the "derivatives" correspond to the "molecules" in claims 1-3, 25, 26 and 29.

(ii) Applicants have amended claims 2-3, 25-26 and 29 to delete the word "its". Applicant submits that there is now proper antecedent for "the amine" in claims 2-3, 25, 26 and 29. Applicant has amended claim 19 to provide a proper antecedent for "the amine" in claim 20.

(iii) Applicants have deleted the second "comprising " from claim 25 and specified that the first "comprising" relates to "the sample".

(iv) Applicants have amended claim 27 to set forth the steps involved. Applicants have added new claims 30 and 31 which are directed to the use of a mass spectrometer reciting analogous method steps as those of claims 2 and 3 respectively.

In light of the amendments and the arguments presented, Applicants submit that the rejections under 35 U.S.C. §112 has been obviated and therefore request that the rejections be withdrawn.

### **Claim Rejections under 35 U.S.C. §102**

The Examiner has rejected claims 2-6, 8-15, 17-23, 25 and 29 as allegedly anticipated by Aebersold et al. (US 6,670,194) (hereinafter "Aebersold et al.").

To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1379 (Fed. Cir. 1986).

Applicants have amended claims 1, 2, 3, 24, 25, 26, 27 and 29 by inserting the term, "without use of an affinity group." Applicants submit that labeling without the use of the affinity group is not taught by Aebersold et al.

As discussed in the previous response to office action, Aebersold et al. discloses a method to analyze proteins using a multi-component protein reactive reagent of the formula A-L-PRG, where A is an affinity label (also known as an affinity group) that selectively binds to a capture reagent, L is a linker group which is differentially labeled with one or more stable isotopes and PRG is a "protein reactive group" that selectively reacts with a protein functional group or is a substrate for an enzyme. Accordingly, in the method of Aebersold et al. the linker is labeled, not the protein reactive group (PRG).

For example, Aebersold et al. describes the use of an aldehyde in the context of a protein reactive group (PRG) (col. 10, lines 50-52) which would then be coupled to an isotope labeled linker (L) (col. 9, lines 60-65) and an affinity group. However, in the present invention, the isotope label (L), as well as the covalent attachment to the protein (A), is combined in one molecule (i.e., the aldehyde), thereby there is only a one component system employed in the instant invention. This greatly simplifies the chemistry involved while, at the same time, achieving the goal of attaching different isotopic labels to different protein samples. The

practical advantage of simple chemistry is that the differential reagents described here do not interfere with subsequent mass spectrometric analysis as a result of their small size. Indeed the technique taught by Aebersold et al. and sold by Applied Biosystems as "ICAT" reagents has been replaced by a "cleavable ICAT" reagent (a copy of which is enclosed for the Examiner's convenience) that involves removal of the affinity group after affinity purification to reduce interference with mass spectrometric detection.

Additionally, Aebersold et al. use a linker group containing isotopes, specifically deuterium atoms, attached to aliphatic carbons to produce differential reagents (i.e.  $-\text{CH}_2-$  or  $-\text{CD}_2-$ ), such as in Aebersold et al. schemes 1, 2, 19 and 21. In contrast, the present invention involves placement of deuterium and/or carbon-13 in methyl amine ( $\text{N}-(\text{CH}_3)_2$  or  $\text{N}-(\text{CD}_3)_2$ ). The advantage of placement of the isotopes at this position is that the derivatized molecules co-elute under reverse phase chromatography (see Figure 6B in the current application) whereas the reagent described by Aebersold et al. do not co-elute. Indeed, in the "cleavable ICAT" reagent mentioned above, carbon-13 is used in place of deuterium to improve chromatographic co-elution.

In addition, as discussed in paragraph [0074], the present invention can produce up to eight isotopically unique reagents by the use of formaldehyde, deuterated formaldehyde, carbon-13 formaldehyde, carbon-13/deuterated formaldehyde, sodium cyanoborohydride and sodium cyanoborodeuteride, in a simple, one-step reaction. Therefore, the present invention could be used to analyze up to eight samples simultaneously. Although Aebersold et al. state in claim 1 that the technology can be used for two or more samples, Aebersold et al. do not provide sufficient information or any examples of reagents that are capable of analyzing more than two samples.

Given that Aebersold et al. and co-authors describe reagents with amines bearing active hydrogens such as primary amines (Aebersold et al. scheme 3 contains a  $-\text{NH}_2$  group) and also methyl amines (Aebersold et al. scheme 13 contains a  $-\text{N}-(\text{CH}_3)$  group) but do not describe

isotopic derivatization of these amines and the resulting increased performance, demonstrates that the technology claimed in the instant application was not taught by Aebersold et al.

Further, the present invention does not employ a separate affinity group (A). The use of a separate affinity tag and a linker is a central component of the technology developed by Aebersold et al. They elaborate on the beneficial effects of selective enrichment (col. 14, lines 47-50). Accordingly, Applicants submit that the multi-component system disclosed in Aebersold et al. employs an affinity group and linker group, and does not anticipate the presently claimed invention.

In the the office action, the Examiner states that "Applicants' argument has been carefully considered by is not persuasive because such a negative claim limitation, i.e. an invention that 'does not employ an affinity label and a linker group', is not recited anywhere in Applicants' claims". Accordingly, Applicant has amended the claims by reciting the limitation (i.e. "without use of an affinity group"). As such, Applicants respectfully request withdrawal of this rejection.

#### **Rejections under 35 U.S.C. 103(a)**

Claims 1, 4-15, 17-24 and 26-27 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Aebersold et al. (US 6,670,194) in view of Figeys et al. (US 2002/0076817) (hereinafter "Figeys et al.").

Claim 16 stands rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Aebersold et al. (US 6,670,194) and Figeys et al. (US 2002/0076817) as applied to claims 1 and 15 and further in view of Vandekerckhove & Gevaert (US 2004/0005633) (hereinafter "Vandekerckhove").

First, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, a prior art reference (or references) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

**A. Aebersold et al. in view of Figeys et al.**

As described above, Aebersold et al. does not teach the method as currently claimed. Further, the teachings of Aebersold et al. cannot have suggested the currently claimed invention due to the complexity of the multi-component system employed in Aebersold et al. In fact, the teachings of Aebersold et al. teaches away from the currently claimed invention of a simple, one-step reaction *without an affinity group*.

The citation of Figeys et al. does not cure this defect. First, Figeys et al. does not supply the necessary teachings to arrive at the currently claimed invention of a simple, one-step reaction. Second, as described in the previous response, Figeys et al. uses different proportions of two isotopically distinct components, not two chemically distinct compounds.

Accordingly, the claims are not obvious in view of Aebersold et al. and Figeys et al. Specifically, the limitation of "without use of an affinity group" has not been met by the combination of Aebersold et al. and Figeys et al.

**B. Aebersold et al. and Figeys et al. further in view of Vanderkerckhove**

The Examiner has rejected claim 16 on the basis of obviousness with regard to Aebersold et al. (US 6,670,194) in view of Figeys (US 2002/0076817) and Vandekerckhove and Gevaert (US 2004/0005633).

For the same reasons as described above, the combination of Aebersold et al. and Figeys et al. does not teach the methods of the claims. Vandekerckhove teaches another multi-step procedure that requires the peptides be separated into fractions prior to any chemical alteration.



(col. 1, paragraph [003]). Accordingly, the combination of Aebersold et al., Figeys et al. and Vandekerckhove does not teach the method of dependent claim 16.

In light of the arguments presented above, Applicants respectfully request that both rejections under 35 U.S.C. §103 be withdrawn.

### **Conclusion**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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